

5,705,518) in view of Levy et al. (U.S. Patent No. 5,283,255). Applicants respectfully traverse.

In the present case, the Examiner maintains that Applicants have argued against the cited references individually which cannot show non-obviousness. Contrary to the Examiner's assessment of Applicants' arguments, Applicants acknowledge in the reply to the previous office action that Levy was used to modify Richter (see page 3, 3<sup>rd</sup> full paragraph of the reply filed June 13, 2002). Thus, Applicants have not attempted to show non-obviousness by attacking the references individually. Rather, Applicants have shown the deficiencies in Richter which, if modified by Levy, fail to teach or suggest the present invention.

The present invention relates to a photodynamic therapy treatment of a patient suffering from a disorder associated with an agent of exogenous origin, characterized by skin lesions, involving administration of a precursor of protoporphyrin IX followed by exposure of the agent of exogenous origin to light capable of photoactivating protoporphyrin IX. The present invention includes administration of an agent, such a precursor of protoporphyrin IX, which is not itself a photosensitizer, but induces the synthesis or accumulation of protoporphyrin IX in vivo. See, for example, specification page 7, lines 14-22.

For a proper *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. See MPEP 2142.

In the present case, the Examiner suggests that Levy can be used to modify Richter because Levy teaches administration of a exogenous photosensitizer, a green porphyrin, for use in photodynamic therapy of a fungal infection, tinea pedis. It is this teaching in Levy which can allegedly modify Richter's disclosure of administration of 5-ALA to a patient with papilloma virus.

The Examiner asserts that Richter teaches using 5-aminolevulinic acid (5-ALA) to treat skin infections such as papilloma virus. Applicants note that Richter discloses that papilloma virus is effectively treated with a photosensitizer such as 5-ALA because the drug targets "areas of neovascularization" (see claims of Richter). Fungi do not have vessels, and therefore, fungi cannot be areas of neovascularization. Therefore, Richter does not teach PDT in a patient who is suffering from a disorder associated with an agent of exogenous origin, where that agent of exogenous origin is fungus.<sup>1</sup>

The Examiner uses Levy to remedy the lack of teaching of treatment of a skin disorder associated with an agent of exogenous origin, wherein the agent of exogenous origin is fungus. Levy teaches the use of a group of hydromonobenzoporphyrins or "green porphyrins." These are externally formed, exogenous photosensitizers which are applied to the patient primarily by injection (because of their high molecular weight). With these compounds, the photoactive agent is administered directly and in final form, so achieving a photodynamic response is not dependent on the internal (either organ level or cellular level) synthesis of the actual active compound (as a metabolite). It depends merely on the delivery of the administered compound to the target site. Administration of hydromonobenzoporphyrins differs from administration of the recited "precursor of protoporphyrin IX." As stated above, precursors of protoporphyrin IX (PpIX) are not photosensitizers, but rather induce synthesis or accumulation or both of PpIX in vivo. Therefore, administration of a precursor of PpIX involves administration of an endogenous photosensitizer.

As a specific example, 5-ALA acts as a pro-drug. It is not active in and of itself. Administration of 5-ALA induces the formation at the cellular level within the body of the formation of the actual active photosensitizer (protoporphyrin IX). Because the cellular mechanisms are quite different across the phylogenetic continuum (plants, animals, single cell organisms, etc.), the behavior in the presence of 5-ALA is not the same throughout. Thus, the teaching in Richter of administering 5-ALA for papilloma virus would not provide a reasonable expectation of success in fungus.

<sup>1</sup> Moreover, it is known in the literature that the vascular endothelium in animals does not readily produce protoporphyrin IX; therefore direct vascular effects and the targeting of areas of neovascularization would not encompass treating fungal disorders because fungus are not areas of neovascularization.

Levy, which teaches administration of *exogenous* hydromonobenzoporphyrins, fails to teach or suggest administration of an *endogenous* precursor of protoporphyrin IX for the effective treatment of onychomycosis. It is understood that Levy is meant to modify the teaching of Richter. It is pointed out that Richter specifically discloses administering a photosensitizing agent and provides examples of agents which are themselves photosensitizing agents and mentions 5-ALA as a prodrug. Richter, like Levy, is directed to administration of an exogenous photosensitizing agent to a patient for PDT. Thus, because (1) there is no suggestion in the references themselves of administration of an endogenous photosensitizer for treating disorders associated with an agent of exogenous origin in PDT; (2) there is no reasonable expectation of success since one skilled in the art would not expect that administration of an exogenous photosensitizer would be predictive of administration of an endogenous photosensitizer because administration of an endogenous photosensitizer, in the present case, a precursor of PpIX, would not be expected to be effective in treating disorders associated with fungus since it is not an area of neovascularization; and (3) Richter and Levy fail to teach all the claim elements. Accordingly, not only does the art fail to teach the claimed invention, the references are not properly combinable according to MPEP 2142.

Therefore, because Richter and Levy, when combined, fail to teach or suggest the presently claimed invention, reconsideration and withdrawal of the invention are respectfully requested.

**III. CONCLUSION**

Applicant believes that the present application is now in condition for allowance.  
Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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